Serotonin

Its Possible Relation to Allergic Disease

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• **Increased amounts of serotonin as well as histamine have been found in the blood of animals during anaphylactic shock. Certain animals, particularly those in which antihistamines do not prevent anaphylaxis, have been found to have increased quantities of serotonin in the lung tissue during anaphylactic shock.**

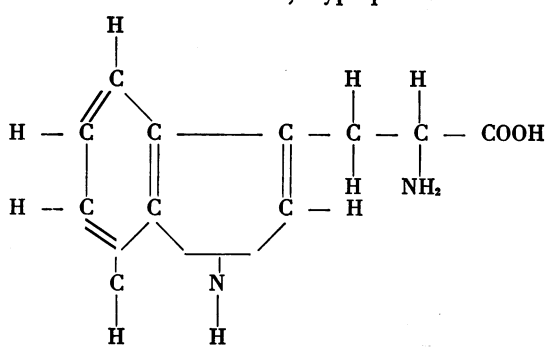
Serotonin is a chemical derived from the amino acid tryptophan, which is widely distributed. It is excreted in the urine as the metabolite 5-hydroxyindoleacetic acid. Serotonin has been found in increased amounts in the blood of patients with carcinoids. The increase of serotonin in the blood and the finding of the excretory product in the urine has become a corroborative sign of the disease. The involvement of serotonin in the production of mental disease is evidenced by the effect of serotonin antagonists, which appear to influence mental behavior.

That serotonin antagonists may be of ultimate value in the treatment of allergic disease is a possibility to be considered.

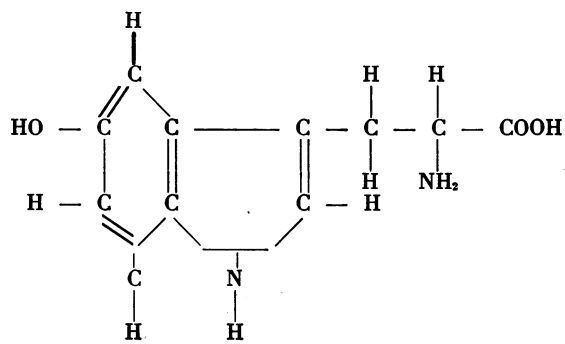
SINCE ITS ISOLATION some 11 years ago, serotonin (5-hydroxytryptamine) has captured the interest of the medical world. It is abundant in the platelets and other cells such as the mast cells of the human body. In nature, it has been found in bacterial pigments, in the salivary gland of the octopus and in the venum of tropical toads. It has been liberated from plants and is said to have been used by primitive people to produce trance-like states for ritual purposes.

The history of how serotonin was isolated and reports on where it is found, its significance and analytical determination are most interesting. The isolation and identification of serotonin was performed by two research teams working independently. Priority belongs to Rapport, Green and Page.[15] They isolated it from beef serum in 1948. At that time, a colleague of theirs, Corcoran, coined the term *serotonin* for this substance and later, in a letter to the *Journal of the American Medical Association*,[3] advocated the exclusive use of this term. Three years later, Erspamer[4] identified enteramine, a vasoconstrictor which he had been studying as a hormone of the enterochromaffin system, as 5-hydroxytryptamine and noted that it was identical with the compound isolated by Rapport and coworkers.

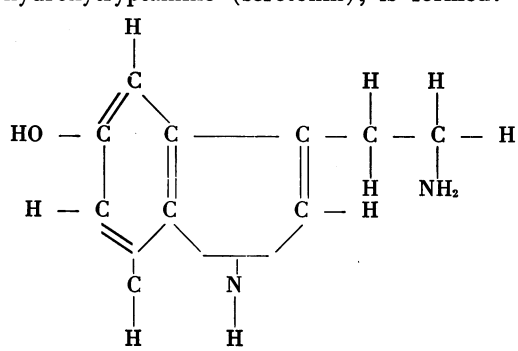
Serotonin is easily synthesized. The precursor is the common amino acid, tryptophan:



By addition of a hydroxyl group in the 5 position, a change which is presumed to take place in the liver, the immediate precursor of 5-hydroxytryptophan, is formed:



Finally, by loss of carbon dioxide from the amino group, which probably occurs in the wall of the intestinal tract, the liver, the kidney and presumably the brain also, the ultimate compound, 5-hydroxytryptamine (serotonin), is formed:



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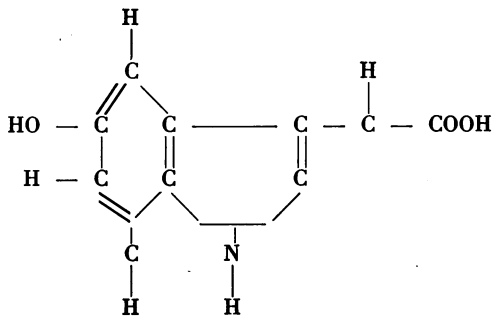
The inactivated excretory product, 5-hydroxyindoleacetic acid, is formed by oxidation and removal of the amino group by the enzyme, amine oxidase:



There are numerous ramifications of the physiological activity of serotonin. It is said to be involved in abnormal mental behavior, in microcirculation of the skin, in renal function, in muscular activity, in vasodilatation of the pulmonary circulation, in bronchoconstriction and in intestinal tumors. Lembeck[12] found that carcinoid tumors called argentiffinomas (because of their characteristic staining with silver) contained large amounts of serotonin. He speculated that an overproduction of serotonin, with subsequent serotonemia, could be an important and reliable diagnostic sign in this condition. Tests were devised to determine the amount of serotonin in the blood,[19] and of the breakdown product, 5-hydroxyindoleacetic acid in the urine.[18] These tests are now routinely used.

Much of the current research on serotonin is concerned with its physiological effect on the central nervous system, where it appears to influence mental processes. For those interested in allergic diseases it is important because of the fact that it is present and is a bronchoconstrictor of the lungs of certain animals during anaphylaxis[21] together with the enzymes which make and destroy it, as well as in the blood stream in company with histamine.[20]

Clinically, the first suggestion that serotonin might be implicated in allergic diseases was the report of Waldenstrom's group.[17] Thorsen, Waldenstrom and co-workers described several cases of metastatic, malignant carcinoid tumors in several of which asthma was a part of the clinical picture. One case was that of a 19-year-old boy, who from the age of six had dyspnea upon exertion and who had been hospitalized in three successive years, when he was nine, ten and eleven. Another case was that of a 63-year-old man, who for nine years until two years before he died had attacks of nocturnal dyspnea, with wheezing respiration and cough which were relieved by injections of epinephrine. In another case a 43-year-old woman had had wheezing and shortness of breath for three years, from the age of 37 to 40, which was diagnosed as asthma. It is assumed that the asthma in these cases was due to the bronchoconstricting activity of serotonin since later these research workers were able to reproduce all the clinical symptoms, including asthma, by administration of serotonin.

In animal experimentation, when serotonin is inhaled by a guinea pig as a 1 per cent aerosol, bronchial spasm with severe dyspnea followed by convulsions results.[7] Duration of the exposure and symptoms are the same as those which occur with aerosols of 0.5 per cent histamine phosphate, or 0.25 per cent acetylcholine. Since Neo-Antergan (pyrilamine) completely protects against histamine and gives considerable protection in guinea pigs against anaphylactic shock, it was thought that it might antagonize serotonin activity as well. However, 1 mg. per kilogram of body weight of Neo-Antergan when injected into the guinea pig one hour before aerosol administration, produced no anti-serotonin activity. On the other hand, atropine sulphate, 0.32 mg. per kilogram of body weight, which protects against the effects of acetylcholine, and very slightly against anaphylactic shock, rendered considerable protection against serotonin activity. This would appear to suggest that the effects of serotonin in producing bronchospasm in the guinea pig are purely of a chemical nature and not necessarily involved in the anaphylactic reaction as a result of antigen-antibody union.

In an analysis of the actual presence of serotonin in the lung, and in an attempt to evaluate its implication in the pulmonary aspects of anaphylaxis, Weissbach, Waalkes and Udenfriend[21] presented some interesting data. Measuring the amounts of serotonin in the lungs of various animals that had been sensitized, and then shocked to produce an anaphylactic reaction, they found a decided difference in the quantities, the difference depending upon the kind of animal used. They noted that guinea pig lungs contain little serotonin, while the lungs of mice, rats and rabbits contain relatively large amounts. These findings were in sharp contrast with the amount of histamine found in the lungs of similarly shocked animals. Guinea pig lung has been shown to contain comparatively large amounts of histamine, while mouse lung contains little. It is postulated that this explains why in guinea pigs anaphylaxis is readily prevented by pre-treatment with histamine antagonists, while anti-histaminic drugs have little if any effect on anaphylactic shock in mice. One might infer that other animals may have serotonin alone, or perhaps a combination of serotonin and histamine, released as the agents responsible for the symptoms of anaphylactic shock.

One cannot evaluate human anaphylaxis on the basis of results of animal experimentation alone. In animals, it has been traditional to consider one

shock organ as a constant site of the antigen-antibody reaction, the shock organ varying with the kind of animal involved. In guinea pigs the symptoms have been described as due to bronchoconstriction, the animal dying in asphyxia. In rabbits, spasm of the pulmonary arterioles appear to be the result of anaphylactic shock, with the animal usually reported as dying a characteristic "liver death" from dilatation of the portal veins. This exact choice of shock organs, however, is not always constant. Rabbits, which should die of right heart failure, have been reported dying from asphyxia in some cases.

As might be expected, the human shock organ shows even less constancy.

In reviewing autopsies performed on humans who died of anaphylaxis, Kojis[10] found several who died of the guinea pig type, several of the dog type, one of the rabbit type and one of a combination of the guinea pig and dog type. In a case of anaphylactic death following skin tests for allergic sensitivity, which a colleague and I had occasion to study,[6] the patient showed predominantly the guinea pig type of response, although there were elements of other types which could not be ruled out completely. It is clear that, although the guinea pig type appears to predominate, humans have no constant kind of shock tissue response to anaphylactic reactions. If humans could be subjected to experimentation with fatal anaphylaxis, it might be shown that no one type would predominate; that anaphylaxis in the human might resemble any animal type, or a combination of them.

To determine if serotonin was capable of producing clinical asthma in humans, assuming that it is released during an antigen-antibody reaction, Herxheimer[7] subjected ten subjects to the inhalation of 0.67 per cent serotonin for 60 seconds. Four of his subjects were healthy persons with no history of asthma. In those, there was no effect on vital capacity or expiratory speed, no dyspnea and no evidence of asthma. Of the remaining six patients, who were chronic asthmatics in a remission, three had a pronounced attack of asthma following the inhalation of the serotonin and two had respiratory difficulty just short of clinical asthma. This indicated that the effect of serotonin in man is similar to that of histamine and acetylcholine: It is claimed by many investigators that an attack of asthma can be provoked in chronic asthmatic persons by these agents, but not in the normal individual.[16] Herxheimer's study further implicates serotonin as a possible influence in the production of asthma due to allergic reaction.

On the other hand, it has been shown that when dealing with *isolated* human bronchioles, serotonin not only does not constrict them, but large doses actually relax them. This is not true of other animal species, notably the cat, for example, whose isolated bronchioles contract vigorously when subjected to quite low concentrations.[2] In this situation, however, one is dealing with *isolated* bronchioles. Of more importance, probably, is the fact that when serotonin is continuously infused in man, it has been shown that destruction takes place at a high rate in the blood stream. When destruction is prevented by 5-hydroxytryptophane, the accumulated serotonin produces severe diarrhea, but no dyspnea, either of bronchomotor or vasomotor origin.[13] However, it is well known that certain drugs when injected into the human body do not always have the same effect as the same drugs elaborated within the human body. Histamine, for example, recognized as one of the chemicals liberated in the anaphylactic reaction, often produces symptoms that cannot be duplicated by injection or other form of administration.

There is another study which at first glance also appears to contradict the importance of serotonin in allergy diseases. This is the report of Mohler[14] who analyzed 1120 random urine specimens from hospital patients for 5-hydroxyindoleacetic acid. None of the specimens showed the metabolite to be present. This report included 1023 patients in a normal hospital population. Although it is unlikely that many cases of carcinoid tumors were present, it is very probable, in light of the comparatively high prevalence of allergic disease among the general population, that a large percentage of these patients had allergic sensitivity and had some dormant if not active form of allergic disease. Such a study might prove that the urinary finding of the breakdown product of serotonin is an excellent test for carcinoid, but not exact enough for allergic disease.

Another interesting recent study is that of Berg and Westermeyer.[1] They examined the urine specimens of 52 asthmatic persons for 5-hydroxyindoleacetic acid and found that it was present in a varying degree, the variation according with the severity of the asthma. They expressed belief that this is due to the presence of an elusive substance in the urine which is difficult to isolate, but which combines with 5-hydroxyindoleacetic acid in the urine to form a complex which dissociates under certain conditions. Although this may be the case, it is also possible that serotonin is not excreted in the severe cases, but is stored in the lungs or in the blood and tissue cells in asthma.[22] This may be the explanation, at least in part, for the absence of the metabolite in the urine of patients with asthma.

More pertinent to the practicing physician who treats patients with allergic sensitivity is the possibility that a serotonin antagonist might be found which would neutralize the effect of serotonin, pro-

vided it shall be conclusively proven both that serotonin is released during the course of an antigen-antibody reaction in humans and that it is of importance in the production of asthma or some other manifestation of the allergic state. In the study of mental disease, many drugs have been tested for their anti-serotonin activity. These include reserpine, LSD (lysergic acid diethylamide), and BAS (1-benzyl-2-methyl-5-methoxytryptamine), which is the benzyl analogue of serotonin. Experiments with the latter seem to verify that anti-serotonin activity may be in the form of a true displacement of the chemical from tissue by a specific metabolite. That an intermediary metabolite is involved as well, is suggested by the fact that parenteral use of serotonin produces peripheral symptoms, but no symptoms referable to the central nervous system. When given parenterally, serotonin does not pass the blood-brain barrier.

A group of serotonin antagonists were also investigated by King.[9] He perfused the lungs of guinea pigs to test the antagonism of these drugs to bronchoconstriction brought about by doses of 12.5 to 40 micrograms of serotonin. The following drugs were tested: chlorpromazine hydrochloride, BOL-148 ('2-brom-d-lysergic acid diethylamide), narcotine hydrochloride and Sandostene (methyl-aminophenyl-thenyl-piperidine tartrate). Sandostene was the most effective. In doses of 250 micrograms it was capable of completely antagonizing bronchoconstriction.

It is noteworthy that excellent results have been reported in the clinical treatment of asthma with Sandostene plus calcium.[11] Gaynes and Shure[5] reported excellent results with this drug in the treatment of allergic pruritis. It is speculated that these good therapeutic results may have been due to the anti-serotonin activity of Sandostene.

No definitive statement can be made as to the actual effectiveness of serotonin antagonists. The problem is a complicated one. Antagonism is not merely the conversion of a chemical radical; it involves anti-metabolic processes which probably require occupation of the specific receptors normally used by the metabolite that is being replaced.

It is clear that much more data must be obtained before a satisfactory answer can be given to the question whether or not serotonin is implicated in diseases of allergy in humans. This problem is intriguing many medical research teams throughout the world, some of whom have been quoted in this communication. The results of their research will be watched closely. To quote Beckman:[23] "The picture is still blurred and it is too soon to know whether the completed canvas will be truly representational or merely a non-objective presentation that is pleasing, but in itself not significant. Nevertheless, I look upon these serotonin-LSD developments as the two most important of current pharmacological topics—although neither of the two agents is actually a drug." What Beckman said in 1957 is applicable in 1959.

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